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Title: Limitations in the Application of Clinicopathologic Factors Alone in Predicting Radiation Benefit for Women with Low-Risk DCIS after Breast Conserving Surgery: The Impact of a 7-gene Biosignature based on 10-year Ipsilateral Breast Recurrence (IBR) Rates

Background: Most women diagnosed with ductal carcinoma in situ (DCIS) receive radiotherapy (RT) after breast-conserving surgery (BCS); however, clinical trials show that over 70% of women with BCS alone will not have a recurrence and therefore not benefit from RT. Traditionally, clinicopathologic (CP) factors have been used to select for whom to de-escalate treatment, but prospective trials have failed to identify a low risk CP group that did not benefit from RT with respect to local control. This study assessed the reclassification of patients with low-risk CP into Risk groups defined by the 7-gene biosignature and compared to 10-yr IBR rates.

Material and Methods: Women (n=926) from four international DCIS cohorts treated with BCS had formalin fixed paraffin embedded tissue samples analyzed at a CLIA lab (Laguna Hills, CA). CP low-risk patients were identified using a) RTOG-9804-like criteria [Nuclear Grade 1 or 2 & Size ≤2.5 cm & non-Palpable & Screen Detected & margin negative (no-ink on tumor)] and b) MSKCC-like criteria [low-risk score<220, determined using nomogram weighted factors (excluding: number of re-excisions and RT treatment), and using no-ink-on-tumor instead of close margin]. The 7-gene DCIS biosignature combined biomarkers with CP factors (age, size, palpability, and margin status) using an algorithm reporting a Decision Score (DS) and Residual Risk subtype (RRt). Women with low-risk CP were classified into biosignature Low Risk (DS≤2.8, no RRt) or High Risk (DS>2.8 +/- RRt) groups. 10-year in-breast event (IBR) rates with and without RT were assessed by Kaplan-Meier rates and Cox proportional hazard analyses.

Results: Overall, 37% of all women were classified into the biosignature Low Risk group, while 51% and 34% were classified into CP low-risk groups (RTOG-9804-like, MSKCC-like, respectively). The biosignature Low Risk group (n=338) had a 10-yr IBR risk of 5.6% after BCS and no significant RT benefit (absolute RT benefit=0.8%, p=0.70), 99% negative predictive value (NPV) for RT benefit. CP low-risk groups had 10-yr IBR rates of 12% and 8% after BCS without RT with absolute 6% (p=0.04) and 4% (p=0.1) IBR rate reductions with RT. The biosignature reclassified 51% and 63% of CP low-risk patients into the biosignature High Risk group. Importantly, these patients had higher IBR rates without RT (20% and 12%) and significant 13% (p=0.005) and 8% (p=0.01) absolute IBR rate reductions from RT. CP low-risk patients with concordant biosignature Low Risk demonstrated no significant RT benefit.

Conclusion: The 7-gene predictive biosignature more reliably identified patients with low 10-yr IBR rates and no significant RT benefit than the traditional CP low-risk criteria (RTOG-9804-like, MSKCC-like). Importantly, those CP low-risk patients who were re-classified as biosignature High Risk had increased 10-year IBR rates and significant RT benefit.

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